

CLAIMS

1. A compound having the formula A-(LM)-C, wherein A is a Factor VIIa (FVIIa) polypeptide; LM is an optional linker moiety; and C comprises an immunostimulatory effector domain; and
5 wherein said compound binds to tissue factor (TF).
2. The compound according to claim 1, wherein said compound inhibits TF-mediated FVIIa activity.
- 10 3. The compound according to claim 1, wherein A is a FVIIa polypeptide that is catalytically inactivated in the active site.
4. The compound according to claim 3, wherein A is catalytically inactivated in the active site with a chloromethyl ketone inhibitor independently selected from the group consisting of Phe-
15 Phe-Arg chloromethyl ketone, D-Phe-Phe-Arg chloromethyl ketone, L-Phe-Phe-Arg chloromethyl ketone, Phe-Pro-Arg chloromethyl ketone, D-Phe-Pro-Arg chloromethyl ketone, L-Phe-Pro-Arg chloromethyl ketone, Glu-Gly-Arg chloromethyl ketone, L-Glu-Gly-Arg chloromethyl ketone, D-Glu-Gly-Arg chloromethyl ketone, Dansyl-Phe-Phe-Arg chloromethyl ketone, Dansyl-D-Phe-Phe-Arg chloromethyl ketone, Dansyl-L-Phe-Phe-Arg chloromethyl ketone, Dansyl-Phe-Pro-Arg chloromethyl ketone, Dansyl-D-Phe-Pro-Arg chloromethyl ketone, Dansyl-L-Phe-Pro-Arg chloromethyl ketone, Dansyl-Glu-Gly-Arg chloromethyl ketone, Dansyl-L-Glu-Gly-Arg chloromethyl ketone, and Dansyl-D-Glu-Gly-Arg chloromethyl ketone.
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5. The compound according to claim 1, wherein A is native human FVIIa or a fragment thereof.
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6. The compound according to claim 5, wherein A is native human FVIIa.
7. The compound according to claim 1, wherein C comprises a molecule selected from the group consisting of: mannose binding protein (MBP); proteins with carbohydrate residues that interact with the mannose-fucose receptor of phagocytes; opsonins; proteins capable of recognition by receptors on scavenger macrophages; ligands for integrins normally located on phagocytes; and glycoproteins comprising a Gal-Gal epitope recognized by macrophages.
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8. The compound according to claim 1, wherein C comprises an immunoglobulin molecule or fragment thereof.
9. The compound according to claim 1, wherein C comprises an immunoglobulin molecule.
- 5 10. The compound according to claim 8, wherein C comprises an Fc domain of an immunoglobulin molecule or fragment thereof.
- 10 11. The compound according to claim 8, wherein the immunoglobulin molecule is selected from the group consisting of IgG1, IgG2, IgG3, IgM, IgA, IgE and IgD.
12. The compound according to claim 11, wherein the immunoglobulin molecule is selected from the group consisting of IgG1 and IgG3.
- 15 13. The compound according to claim 8, wherein the immunoglobulin molecule is fully human.
14. The compound according to claim 8, wherein the immunoglobulin molecule is an anti-FVII antibody.
- 20 15. The compound according to claim 14, wherein the anti-FVII antibody does not inhibit FVII/TF complex formation.
16. The compound according to claim 1, wherein C comprises the sequence of SEQ ID NO:7.
- 25 17. The compound according to claim 1, wherein the compound with the formula A-(LM)-C comprises the sequence of SEQ ID NO:8.
- 30 18. The compound according to claim 1, wherein C or (LM)-C is conjugated to oligosaccharides present on the FVIIa polypeptide.
19. The compound according to claim 1, wherein C or (LM)-C is conjugated to a free sulfhydryl group present on the FVIIa polypeptide.
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20. The compound according to claim 1, wherein the compound comprises more than one binding site for TF.
21. The compound according to claim 1, wherein LM comprises an amino acid sequence.
22. The compound according to claim 21, wherein the LM comprises the amino acid sequence (Gly-Gly-Gly-Gly-Ser)_n, wherein n is any integer from 1 to 10.
23. The compound according to claim 1, wherein LM comprises a molecule selected from the group consisting of: straight or branched C₁₋₅₀-alkyl, straight or branched C₂₋₅₀-alkenyl, straight or branched C₂₋₅₀-alkynyl, a 1 to 50 -membered straight or branched chain comprising carbon and at least one N, O or S atom in the chain, C₃₋₈cycloalkyl, a 3 to 8 -membered cyclic ring comprising carbon and at least one N, O or S atom in the ring, aryl, heteroaryl, amino acid, wherein the molecules are optionally substituted with one or more of the following groups: H, hydroxy, phenyl, phenoxy, benzyl, thienyl, oxo, amino, C₁₋₄-alkyl, -CONH₂, -CSNH₂, C₁₋₄ monoalkylamino, C₁₋₄ dialkylamino, acylamino, sulfonyl, carboxy, carboxamido, halogeno, C₁₋₆ alkoxy, C₁₋₆ alkylthio, trifluoroalkoxy, alkoxycarbonyl, haloalkyl.
24. The compound according to claim 1, wherein LM comprises a chloromethyl ketone inhibitor independently selected from the group consisting of Phe-Phe-Arg chloromethyl ketone, D-Phe-Phe-Arg chloromethyl ketone, L-Phe-Phe-Arg chloromethyl ketone, Phe-Pro-Arg chloromethyl ketone, D-Phe-Pro-Arg chloromethyl ketone, L-Phe-Pro-Arg chloromethyl ketone, Glu-Gly-Arg chloromethyl ketone, L-Glu-Gly-Arg chloromethyl ketone, D-Glu-Gly-Arg chloromethyl ketone, Dansyl-Phe-Phe-Arg chloromethyl ketone, Dansyl-D-Phe-Phe-Arg chloromethyl ketone, Dansyl-L-Phe-Phe-Arg chloromethyl ketone, Dansyl-Phe-Pro-Arg chloromethyl ketone, Dansyl-D-Phe-Pro-Arg chloromethyl ketone, Dansyl-L-Phe-Pro-Arg chloromethyl ketone, Dansyl-Glu-Gly-Arg chloromethyl ketone, Dansyl-L-Glu-Gly-Arg chloromethyl ketone, and Dansyl-D-Glu-Gly-Arg chloromethyl ketone, wherein A is catalytically inactivated in the active site with said chloromethyl ketone inhibitor.
25. A pharmaceutical composition comprising (i) an amount of a compound having the formula A-(LM)-C, wherein A is a FVIIa polypeptide; LM is an optional linker moiety; C comprises an immunostimulatory effector domain; and wherein said compound binds to TF; and (ii) a pharmaceutically acceptable carrier or excipient.

26. A compound for use as a medicament having the formula A-(LM)-C, wherein A is a FVIIa polypeptide; LM is an optional linker moiety; C comprises an immunostimulatory effector domain; and wherein said compound binds to TF.
- 5 27. A method for preventing or treating disease or disorder associated with pathophysiological TF activity, said method comprising contacting a TF expressing cell with a compound having the formula A-(LM)-C, wherein A is a FVIIa polypeptide; LM is an optional linker moiety; C comprises an immunostimulatory effector domain; and wherein said compound binds to TF.
- 10 28. A method according to claim 27, wherein said disease or disorder associated with pathophysiological TF activity is selected from the group consisting of: deep venous thrombosis, arterial thrombosis, post surgical thrombosis, coronary artery bypass graft (CABG), percutaneous transdermal coronary angioplasty (PTCA), stroke, cancer, tumor metastasis, angiogenesis, ischemia/reperfusion, rheumatoid arthritis, thrombolysis, arteriosclerosis and restenosis following angioplasty, acute and chronic indications such as inflammation, septic chock, septicemia, hypotension, adult respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC), pulmonary embolism, platelet deposition, myocardial infarction, or the prophylactic treatment of mammals with atherosclerotic vessels at risk for
- 15 thrombosis, wherein said method comprises administering a therapeutically effective amount of said compound in combination with a pharmaceutical acceptable excipient and/ or carrier, to a mammal in need of such a treatment.
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